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Epinephrine (also referred to as **adrenaline**; *see Terminology*) is a hormone and neurotransmitter. It is a catecholamine, a sympathomimetic monoamine derived from the amino acids phenylalanine and tyrosine. The Latin roots *ad-* "renew" and the Greek roots *epi-* *nephras* both literally mean "on/to the kidney" (referring to the adrenal gland, which sits atop the kidneys and secretes epinephrine). Epinephrine is often shortened to **epi** or to **EP** in American medical jargon.

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History

Epinephrine was isolated and identified in 1895 by Napoleon Cybulski, a Polish physiologist. In May 1896, William Bates reported the discovery of a substance produced by the adrenal gland in the *New York Medical Journal*.^[1] The discovery was repeated in 1897 by John Jacob Abel.^[2]

Jokichi Takamine, a Japanese chemist, independently discovered the same hormone in 1900.^{[3][4]} In 1901 he isolated and purified the hormone epinephrine from cow glands.

Epinephrine was first artificially synthesized in 1904 by Friedrich Stolz.

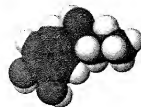
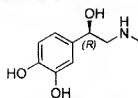
Triggers

Epinephrine is a "fight or flight" hormone, and plays a central role in the short-term stress reaction. It is released from the adrenal glands when danger threatens or in an emergency. Such triggers may be threatening, exciting, or environmental stressor conditions such as high noise levels, or bright light and high ambient temperature (*see Fight-or-flight response*).

Actions in the body

When secreted into the bloodstream, it rapidly prepares the body for action in emergency situations. The hormone boosts the supply of oxygen and glucose to the brain and muscles, while suppressing other non-emergency bodily processes (digestion in particular).

It increases heart rate and stroke volume, dilates the pupils, and constricts arterioles in the skin and gastrointestinal tract while dilating arterioles in skeletal muscles. It elevates the blood sugar level by increasing catabolism of glycogen to glucose in the



(*R*)-(-)-L-Epinephrine or (*R*)-(-)-L-adrenaline

Systematic (IUPAC) name
 (*R*)-4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol

Identifiers

CAS number 51-43-4
 A01AD01 B02BC09
 ATC code C01CA24 R01AA14
 R03AA01 S01EA01
 PubChem 838
 DrugBank APRD00450

Chemical data

Formula C₉H₉NO₃
 Mol. mass 183.204 g/mol

Pharmacokinetic data

Bioavailability Nil (oral)
 Metabolism adrenergic synapse (MAO and COMT)
 Half life 2 minutes
 Excretion Urine

Therapeutic considerations

Pregnancy cat. A(AU) C(US)
 Legal status Prescription Only (S4)(AU)
 POM(UK) R-only(US)
 Routes IV, IM, endotracheal

liver, and at the same time begins the breakdown of lipids in fat cells. Like some other stress hormones, epinephrine has a suppressive effect on the immune system.^[5]

Although epinephrine does not have any psychoactive effects, stress or arousal also releases norepinephrine in the brain. Norepinephrine has similar actions in the body, but is also psychoactive.

The type of action in various cell types depends on their expression of adrenergic receptors.

Mechanism of action

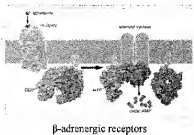


Epinephrine ampule, 1 mg (Supracin[®])

Further reading: adrenergic receptor

Epinephrine's actions are mediated through adrenergic receptors. Epinephrine is a non-selective agonist of all adrenergic receptors. It activates α_1 , α_2 , β_1 , and β_2 receptors.^[6] Specific functions include:

- It binds to α_1 receptors of liver cells, which activate inositol-phospholipid signaling pathway, signaling the phosphorylation of glycogen synthase and phosphorylase kinase (inactivating and activating them, respectively), leading to the latter activating another enzyme—glycogen phosphorylase—which catalyses breakdown of glycogen (glycogenolysis) so as to release glucose to the bloodstream. Simultaneously protein phosphatase-1 (PP1) is inactivated, as in the active state PP1 would reverse all the previous phosphorylations.
- Epinephrine also activates β -adrenergic receptors of the liver and muscle cells, thereby activating the adenylate cyclase signaling pathway, which will in turn increase glycogenolysis.



β_2 receptors are found primarily in skeletal muscle blood vessels where they trigger vasodilation. However, α -adrenergic receptors are found in most smooth muscles and splanchnic vessels, and epinephrine triggers vasoconstriction in those vessels.

Therapeutic use

Epinephrine is used as a drug to treat cardiac arrest and other cardiac dysrhythmias resulting in diminished or absent cardiac output; its action is to increase peripheral resistance via α_1 -adrenoceptor vasoconstriction, so that blood is shunted to the body's core, and the β_1 -adrenoceptor response which is increased cardiac rate and output (the speed and pronouncement of heart beats). This beneficial action comes with a significant negative consequence—increased cardiac irritability—which may lead to additional complications immediately following an otherwise successful resuscitation. Alternatives to this treatment include vasopressin, a powerful antidiuretic which also increases peripheral vascular resistance leading to blood shunting via vasoconstriction, but without the attendant increase in myocardial irritability.^[5]

Due to its suppressive effect on the immune system, epinephrine is the drug of choice for treating anaphylaxis. It is also useful in treating sepsis. Allergy patients undergoing immunotherapy may receive an epinephrine rinse before the allergen extract is administered, thus reducing the immune response to the administered allergen. It is also used as a bronchodilator for asthma if specific beta₂-adrenergic receptor agonists are unavailable or ineffective.

Because of various expression of $\alpha 1$ or $\beta 2$ -receptors, depending on the patient, administration of epinephrine may raise or lower blood pressure, depending whether or not the net increase or decrease in peripheral resistance can balance the positive inotropic and chronotropic effects of epinephrine on the heart, effects which respectively increase the contractility and rate of the heart.

Biosynthesis

Epinephrine is synthesized from norepinephrine in a synthetic pathway shared by all catecholamines, including L-dopa, dopamine, norepinephrine, and epinephrine.

Epinephrine is synthesized via methylation of the primary distal amine of norepinephrine by phenylethanolamine N-methyltransferase (PNMT) in the cytosol of adrenergic neurons and cells of the adrenal medulla (so-called chromaffin cells). PNMT is only found in the cytosol of cells of adrenal medullary cells. PNMT uses S-adenosylmethionine (SAMe) as a cofactor to donate the methyl group to norepinephrine, creating epinephrine.

For norepinephrine to be acted upon by PNMT in the cytosol, it must first be shipped out of granules of the chromaffin cells. This may occur via the catecholamine- H^+ exchanger VMAT1. VMAT1 is also responsible for transporting newly synthesized epinephrine from the cytosol back into chromaffin granules in preparation for release.

Regulation

Epinephrine synthesis is solely under the control of the central nervous system (CNS). Several levels of regulation dominate epinephrine synthesis.

Adrenocorticotrophic hormone (ACTH) and the sympathetic nervous system stimulate the synthesis of epinephrine precursors by enhancing the activity of enzymes involved in catecholamine synthesis. The specific enzymes are tyrosine hydroxylase in the synthesis of dopa and enzyme dopamine- β -hydroxylase in the synthesis of norepinephrine.

ACTH also stimulates the adrenal cortex to release cortisol, which increases the expression of PNMT in chromaffin cells, enhancing epinephrine synthesis. This is most often done in response to stress.

The sympathetic nervous system, acting via splanchnic nerves to the adrenal medulla, stimulates the release of epinephrine. Acetylcholine released by preganglionic sympathetic fibers of these nerves acts on nicotinic acetylcholine receptors, causing cell depolarization and an influx of calcium through voltage-gated calcium channels. Calcium triggers the exocytosis of chromaffin granules and thus the release of epinephrine (and norepinephrine) into the bloodstream.

Epinephrine (as with norepinephrine) does exert negative feedback to down-regulate its own synthesis at the presynaptic alpha-2 adrenergic receptor.

A pheochromocytoma is a tumor of the adrenal gland (or, rarely, the ganglia of the sympathetic nervous system), which results in the uncontrolled secretion of catecholamines, usually epinephrine.

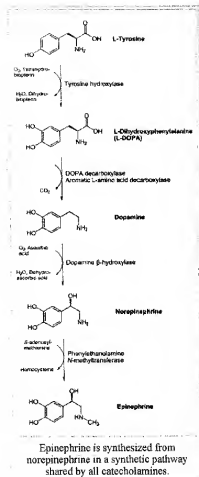
In liver cells, epinephrine binds to the β -Adrenergic receptor which changes conformation and helps Gs, a G protein, exchange GDP to GTP. This trimeric G protein dissociates to Gs alpha and Gs beta/gamma subunits. Gs alpha binds to adenylyl cyclase thus converting ATP into Cyclic AMP. Cyclic AMP binds to the regulatory subunit of Protein Kinase A: Protein kinase A phosphorylates Phosphorylase Kinase. Meanwhile, Gs beta/gamma binds to the calcium channel and allows calcium ions to enter the cytoplasm. Calcium ions bind to calmodulin proteins, a protein present in all eukaryotic cells, which then binds to Phosphorylase Kinase and finishes its activation. Phosphorylase Kinase phosphorylates Phosphorylase which then phosphorylates glycogen and converts it to glucose-6-phosphate.

Side effects and drug interactions

Adverse reactions to epinephrine include palpitations, tachycardia, arrhythmia, anxiety, headache, tremor, hypertension, and acute pulmonary edema.^[7]

Use is contraindicated for patients on β -blockers because severe hypertension and even cerebral hemorrhage may result.^[6]

Terminology



Although widely referred to as *adrenaline* outside of the US, and by the lay public worldwide, the USAN and INN for this chemical is *epinephrine* because *adrenaline* bore too much similarity to the Parke, Davis & Co trademark *Adrenalin* (without the "e") which was registered in the U.S. The BAN and EP term for this chemical is *adrenaline*, and is indeed now one of the few differences between the INN and BAN systems of names.

Amongst U.S. health professionals, the term *epinephrine* is used over *adrenaline*. However, it should be noted that universally, pharmaceuticals that mimic the effects of epinephrine are called *adrenergics*, and receptors for epinephrine are called *adrenoceptors*.

It can also be spelled *epinephrin* (without the "e").

Isomers

Natural epinephrine is the (*R*)-(-)-*L*-epinephrine stereoisomer.

Autoinjectors

Epinephrine is now also used in EpiPens and Twinjects, EpiPens are long narrow autoinjectors that administer epinephrine, Twinjects are similar but contain two doses of epinephrine. It is also used in medicines and usually the Epinephrine is extracted from adrenal glands of hogs, cattle, and sheep.

Though both *EpiPen* and *Twinject* are trademark names, common usage of the terms are drifting toward the generic context of any epinephrine autoinjector.

Pharmaceutical Preparations

Aqueous preparations of adrenaline are obtained by use of hydrochloric acid or tartaric acid, because in the absence of acid medium, it undergoes oxidation.

Borate salt is used in ophthalmology.

See also

- Anaphylaxis
- Adrenaline junkie
- Adrenochrome
- Catechol-O-methyl transferase
- Adrenergic receptor

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Categories: Aromatic compounds | Hormones | Catecholamines | Neurotransmitters | Bronchodilators

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Alzheimer's disease

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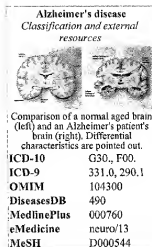
From Wikipedia, the free encyclopedia
(Redirected from Alzheimer)

Alzheimer's disease (**AD**), also called **Alzheimer disease** or simply **Alzheimer's**, is the most common form of dementia. This incurable, degenerative, and terminal disease was first described by German psychiatrist Alois Alzheimer in 1901. Generally it is diagnosed in people over 65 years of age,^[1] although the less-prevalent early-onset Alzheimer's can occur much earlier. An estimated 26.6 million people worldwide were afflicted with Alzheimer's in 2006; this number may quadruple by 2050.^[2]

Although each sufferer experiences Alzheimer's in a unique way, there are many common symptoms.^[3] The earliest observable symptoms are often mistakenly thought to be 'age-related' concerns, or manifestations of stress.^[4] In the early stages, the most commonly recognised symptom is memory loss, such as difficulty in remembering recently learned facts. When a doctor or physician has been notified, and AD is suspected, the diagnosis is usually confirmed with behavioural assessments and cognitive tests, often followed by a brain scan if available.^[5] As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and the general withdrawal of the sufferer as their senses decline.^[6] Gradually, bodily functions are lost, ultimately leading to death.^[7] Individual prognosis is difficult to assess, as the duration of the disease varies. AD develops for an indeterminate period of time before becoming fully apparent, and it can progress undiagnosed for years. The mean life expectancy following diagnosis is approximately seven years.^[8] Fewer than three percent of individuals live more than fourteen years after diagnosis.^[9]

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain.^[10] Currently-used treatments offer a small symptomatic benefit; no treatments to delay or halt the progression of the disease are as yet available. As of 2008, more than 500 clinical trials were investigating possible treatments for AD, but it is unknown if any of them will prove successful.^[11] Many measures have been suggested for the prevention of Alzheimer's disease, but their value is unproven in slowing the course and reducing the severity of the disease. Mental stimulation, exercise, and a balanced diet are often recommended, as both a possible prevention and a sensible way of managing the disease.^[12]

Because AD cannot be cured and is degenerative, management of patients is essential. The role of the main caregiver is often taken by the spouse or a close relative.^[13] Alzheimer's disease is known for placing a great burden on caregivers; the pressures can be wide-ranging, involving social, psychological, physical, and economic elements of the caregiver's life.^[14]^[15] In developed countries, AD is one of the most economically costly diseases to society.^[17]^[18]



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Characteristics

The disease course is divided into four stages, with a progressive pattern of cognitive and functional impairment.

Predementia

The first symptoms are often mistaken as related to ageing or stress.^[4] Detailed neuropsychological testing can reveal mild cognitive difficulties up to eight years before a person fulfills the clinical criteria for diagnosis of AD.^[19] These early symptoms can affect the most complex daily living activities.^[20] The most noticeable deficit is memory loss, which shows up as difficulty in remembering recently learned facts and inability to acquire new information.^{[21][22]} Subtle problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory (memory of meanings, and concept relationships), can also be symptomatic of the early stages of AD.^{[23][24]} Apathy can be observed at this stage, and remains the most persistent neuropsychiatric symptom throughout the course of the disease.^{[25][26][27]} The preclinical stage of the disease has also been termed mild cognitive impairment,^[28] but there is still debate on whether this term corresponds to a different diagnostic entity by itself or just a first step of the disease.^[29]

Early dementia

In people with AD, the increasing impairment of learning and memory eventually leads to a definitive diagnosis. In a small proportion of them, difficulties with language, executive functions, perception (agnosia), or execution of movements (apraxia) are more prominent than memory problems.^[30] AD does not affect all memory capacities equally. Older memories of the person's life (episodic memory), facts learned (semantic memory), and implicit memory (the memory of the body on how to do things, such as using a fork to eat) are affected to a lesser degree than new facts or memories.^{[31][32]} Language problems are mainly characterised by a shrinking vocabulary and decreased word fluency, which lead to a general impoverishment of oral and written language. In this stage, the person with Alzheimer's is usually capable of adequately communicating basic ideas.^{[33][34][35]} While performing fine motor tasks such as writing, drawing or dressing, certain movement coordination and planning difficulties (apraxia) may be present, making sufferers appear clumsy.^[36] As the disease progresses, people with AD can often continue to perform many tasks independently, but may need assistance or supervision with the most cognitively demanding activities.^[30]

Moderate dementia

Progressive deterioration eventually hinders independence.^[30] Speech difficulties become evident due to an inability to recall vocabulary, which leads to frequent incorrect word substitutions (paraphasias). Reading and writing skills are also progressively lost.^{[33][37]} Complex motor sequences become less coordinated as time passes, reducing the ability to perform most normal daily living activities.^[38] During this phase, memory problems worsen, and the person may fail to recognise close relatives.^[39] Long-term memory, which was previously intact, becomes impaired.^[40] and behavioural changes become more prevalent. Common neuropsychiatric manifestations are wandering, sundowning,^[41] irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to caregiving. Approximately 30% of patients also develop illusionary misidentifications and other delusional symptoms.^{[42][25]} Urinary incontinence can develop.^[43] These symptoms create stress for relatives and caretakers, which can be reduced by moving the person from home care to other long-term care facilities.^{[30][44]}

Advanced dementia

During this last stage of AD, the patient is completely dependent upon caregivers. Language is reduced to simple phrases or even single words, eventually leading to complete loss of speech.^[33] Despite the loss of verbal language abilities, patients can often understand and return emotional signals.^[45] Although aggressiveness can still be present, extreme apathy and exhaustion are much more common results.^[30] Patients will ultimately not be able to perform even the most simple tasks without assistance. Muscle mass and mobility deteriorate to the point where they are bedridden,^[46] and they lose the ability to feed themselves.^[47] Finally comes death, usually caused directly by some external factor such as pressure ulcers or pneumonia, not by the disease itself.^{[48][49]}

Pathophysiology

Neuropathology

Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.^[50]

Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD.^[10] Plaques are dense, mostly insoluble deposits of amyloid-beta protein and cellular material outside and around neurons. They continue to grow into insoluble twisted fibres within the nerve cell, often called tangles. Although many older individuals develop some plaques and tangles as a consequence of ageing, the brains of AD patients have a greater number of them in specific brain regions such as the temporal lobe.^[51]

Biochemistry

Alzheimer's disease has been identified as a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain.^[52] Plaques are made up of small peptides, 39–43 amino acids in length, called beta-amyloid (also written as A-beta or A β). Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival and post-injury repair.^{[53][54]} In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis.^[55] One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques.^{[10][56]}

AD is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules. These microtubules act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back. A protein called *tau* stabilises the microtubules when phosphorylated, and is therefore called a microtubule-associated protein. In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system.^[57]

Disease mechanism

Exactly how disturbances of production and aggregation of the beta amyloid peptide gives rise to the pathology of AD has not been elucidated.^[58] The amyloid hypothesis traditionally points to the accumulation of beta amyloid peptides as the central event triggering neuron degeneration. A accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ion homeostasis, induces programmed cell death (apoptosis).^[59] It is also known that A β selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilisation of glucose by neurons.^[60]

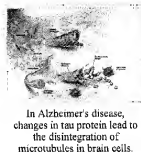
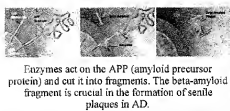
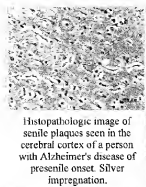
Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer's disease. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response.^[61]

Genetics

While the rare, early-onset form of Alzheimer's disease is mainly explained by mutations in three genes, the most common form has yet to be explained by a purely genetic model. The APOE gene is the strongest genetic risk factor for Alzheimer's discovered so far, but its presence is far from explaining all occurrences of the disease.^[62]

Less than 10% of AD cases occurring before 60 years of age are due to autosomal dominant (familial) mutations, which therefore represent less than 0.01% of all cases.^{[62][63][64]} These mutations have been discovered in three different genes: amyloid precursor protein (APP) and presenilins 1 and 2.^[62] Most mutations in the APP and presenilin genes increase the production of a small protein called Abeta42, which is the main component of senile plaques.^[65]

Most cases of Alzheimer's disease do not exhibit familial inheritance, but genes may act as risk factors. The best known genetic risk factor is the inheritance of the $\epsilon 4$ allele of the apolipoprotein E (APOE). This gene is implicated in up to 50% of late-onset sporadic Alzheimer's cases.^[66] Geneticists agree that numerous other genes also act as risk factors or have protective effects that influence the development of late onset Alzheimer's disease.^[62] Over 400 genes have been tested for



association with late-onset sporadic AD.^[67] One example is a variant of the *reelin* gene that may contribute to Alzheimer's risk in women.^[68]

Causes

Three major competing hypotheses exist to explain the cause of the disease. The oldest, on which most currently available drug therapies are based, is the *cholinergic hypothesis*, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid.^[69] leading to generalised neuroinflammation.^[50]

In 1991, the *amyloid hypothesis* postulates that amyloid beta ($A\beta$) deposits are the fundamental cause of the disease.^{[70][71]} It is a compelling theory because the gene for the amyloid beta precursor (APP) is located on chromosome 21, and people with trisomy 21 (Down Syndrome) who thus have an extra gene copy almost universally exhibit AD by 40 years of age.^{[72][73]} Also APOE4, the major genetic risk factor for AD, leads to excess amyloid buildup in the brain before AD symptoms arise. Thus, $A\beta$ deposition precedes clinical AD.^[74] Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology.^[75] An experimental vaccine was found to clear the amyloid plaques in early human trials, but it did not have any significant effect on dementia.^[76]

Deposition of amyloid plaques does not correlate well with neuron loss.^[77] This observation supports the *tau hypothesis*, the idea that tau protein abnormalities initiate the disease cascade.^[71] In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies.^[78] When this occurs, the microtubules disintegrate, collapsing the neuron's transport system. This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells.^[79]

Diagnosis

Alzheimer's disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions.^{[80][81]} Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia.^[82] Assessment of intellectual functioning including memory testing can further characterise the state of the disease.^[4] Medical organisations have created diagnostic criteria to ease and standardise the diagnostic process for practicing physicians. Sometimes the diagnosis can be confirmed or made at post-mortem when brain material is available and can be examined histologically.^[83]

Diagnostic criteria

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association) established the most commonly used diagnostic criteria for Alzheimer's disease.^[84] These criteria require that the presence of cognitive impairment, and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD. A histopathologic confirmation including a microscopic examination of brain tissue is required for a definitive diagnosis. Good statistical reliability and validity have been shown between the diagnostic criteria and definitive histopathological confirmation.^[85] Eight cognitive domains are most commonly impaired in AD—memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities. These domains are equivalent to the NINCDS-ADRDA Alzheimer's Criteria as listed in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) published by the American Psychiatric Association.^{[86][87]}

Diagnostic tools

Neuropsychological screening tests, such as the mini-mental state examination (MMSE), are widely used to evaluate the cognitive impairments needed for diagnosis. More comprehensive test arrays are necessary for high reliability of results, particularly in the earliest stages of the disease.^{[88][89]} Neurological examination in early AD will usually provide normal results, except for obvious cognitive impairment, which may not differ



Microscopy image of a neurofibrillary tangle, conformed by hyperphosphorylated tau protein



PET scan of the brain of a person with AD showing a loss of function in the temporal lobe

from standard dementia. Further neurological examinations are crucial in the differential diagnosis of AD and other diseases.^[1] Interviews with family members are also utilised in the assessment of the disease. Caregivers can supply important information on the daily living abilities, as well as on the decrease, over time, of the person's mental function.^[90] A caregiver's viewpoint is particularly important, since a person with AD is commonly unaware of his own deficits.^[91] Many times, families also have difficulties in the detection of initial dementia symptoms and may not communicate accurate information to a physician.^[92] Supplemental testing provides extra information on some features of the disease or is used to rule out other diagnoses. Blood tests can identify other causes for dementia than AD^[4]—causes which may, in rare cases, be reversible.^[93] Psychological tests for depression are employed, since depression can either be concurrent with AD or be the cause of cognitive impairment.^{[94][95]}



Neuropsychological screening tests can help in the diagnosis of AD. In them patients have to copy drawings similar to the one shown in the picture, remember words, read or sum.

When available as a diagnostic tool, SPECT and PET neuroimaging are used to confirm a diagnosis of Alzheimer's in conjunction with evaluations involving mental status examination.^[96] The ability of SPECT to differentiate Alzheimer's disease from other possible causes in somebody already known to be suffering from dementia, appears to be superior to attempts to diagnose by mental testing and history.^[97] A new technique known as PIB PET has been developed for directly and clearly imaging beta-amyloid deposits in vivo using a tracer that binds selectively to the Aβ deposits.^[98] Another recent objective marker of the disease is the analysis of cerebrospinal fluid for amyloid beta or tau proteins.^[99] Both advances have led to the proposal of new diagnostic criteria.^{[84][4]}

Prevention

Global studies of measures to prevent or delay the onset of AD have often produced inconsistent results. At present, there appears to be no definitive evidence to support the belief that any particular measure is effective in preventing AD.^[100] However, epidemiological studies have proposed relationships between certain modifiable factors, such as diet, cardiovascular risk, pharmaceutical products, or intellectual activities among others, and a population's likelihood of developing AD. Only further research, including clinical trials, will reveal whether, in fact, these factors can help to prevent AD.^[101]



Intellectual activities such as playing chess or regular social interaction have been linked to a reduced risk of AD in epidemiological studies, although no causal relationship has been found.

The components of a Mediterranean diet, which include fruit and vegetables, bread, wheat and other cereals, olive oil, fish, and red wine, may all individually or together reduce the risk and course of Alzheimer's disease.^[102] Several vitamins such as B12, B3, C or folic acid have been found in some studies to be related to a reduced risk of AD^[103] but other studies indicate that they do not have any significant effect on the onset or course of the disease and may have important secondary effects.^[104] Curcumin from the curry spice turmeric has shown some effectiveness in preventing brain damage in mouse models.^[105]

Although cardiovascular risk factors, such as hypercholesterolemia, hypertension, diabetes, and smoking, are associated with a higher risk of onset and course of AD,^{[106][107]} statins, which are cholesterol lowering drugs, have not been effective in preventing or improving the course of the disease.^{[108][109]} However long-term usage of non-steroidal anti-inflammatory drug (NSAIDs), is associated with a reduced likelihood of developing AD in some individuals.^[110] Other pharmaceutical therapies such as female hormone replacement therapy are no longer thought to prevent dementia,^{[111][112]} and a 2007 systematic review concluded that there was inconsistent and unconvincing evidence that ginkgo has any positive effect on cognitive impairment.^[113]

Intellectual activities such as reading, playing board games, completing crossword puzzles, playing musical instruments, or regular social interaction may also delay the onset or reduce the severity of Alzheimer's disease.^{[114][115]} Bilingualism is also related to a later onset of Alzheimer's.^[116]

Some studies have shown an increased risk of developing AD with occupational exposure to magnetic fields,^{[117][118]} intake of metals, particularly aluminum,^{[119][120]} or exposure to solvents.^[121] The quality of some of these studies has been criticised,^[122] and other studies have concluded that there is no relationship between these environmental factors and the development of AD.^{[123][124][125][126]}

Management

There is no cure for Alzheimer's disease; available treatments offer relatively small symptomatic benefit but remain palliative in nature. Current treatments can be divided into pharmaceutical, psychosocial and caregiving.

Pharmaceutical

Four medications are currently approved by regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat the

cognitive manifestations of AD: three are acetylcholinesterase inhibitors and the other is memantine, an NMDA receptor antagonist. No drug has an indication for delaying or halting the progression of the disease.

Reduction in the activity of the cholinergic neurons is a well-known feature of Alzheimer's disease.^[127] Acetylcholinesterase inhibitors are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons.^[128] As of 2008, the cholinesterase inhibitors approved for the management of AD symptoms are donepezil (brand name *Aricept*),^[129] galantamine (*Razadyne*),^[130] and rivastigmine (branded as *Exelon*^[131] and *Exelon Patch*^[132]). There is evidence for the efficacy of these medications in mild to moderate Alzheimer's disease,^[133] and some evidence for their use in the advanced stage. Only donepezil is approved for treatment of advanced AD dementia.^[134] The use of these drugs in mild cognitive impairment has not shown any effect in a delay of the onset of AD.^[135] The most common side effects are nausea and vomiting, both of which are linked to cholinergic excess. These side effects arise in approximately ten to twenty percent of users and are mild to moderate in severity. Less common secondary effects include muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production.^[136] Glutamate is a useful excitatory neurotransmitter of the nervous system, although excessive amounts in the brain can lead to cell death through a process called excitotoxicity which consists of the overstimulation of glutamate receptors. Excitotoxicity occurs not only in Alzheimer's disease, but also in other neurological diseases such as Parkinson's disease and multiple sclerosis.^[137] Memantine (brand names *Akatinol*, *Axura*, *Ebixa/Abixa*, *Memox* and *Namenda*),^[138] is a noncompetitive NMDA receptor antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate.^[137] Memantine has been shown to be moderately efficacious in the treatment of moderate to severe Alzheimer's disease. Its effects in the initial stages of AD are unknown.^[139] Reported adverse events with memantine are infrequent and mild, including hallucinations, confusion, dizziness, headache and fatigue.^[140] The combination of memantine and donepezil has been shown to be "of statistically significant but clinically marginal effectiveness".^[141]

Antipsychotic drugs are modestly useful in reducing aggression and psychosis in Alzheimer's patients with behavioural problems, but are associated with serious adverse effects, such as cerebrovascular events, movement difficulties or cognitive decline, that do not permit their routine use.^[142]

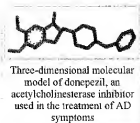
Psychosocial intervention

Psychosocial interventions are used as an adjunct to pharmaceutical treatment and can be classified within behaviour-, emotion-, cognition- or stimulation-oriented approaches. Research on efficacy is unavailable and rarely specific to AD, focusing instead on dementia in general.^[143]

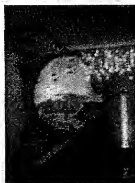
Behavioural interventions attempt to identify and reduce the antecedents and consequences of problem behaviours. This approach has not shown success in improving overall functioning.^[144] but can help to reduce some specific problem behaviours, such as incontinence.^[145] There is a lack of high quality data on the effectiveness of these techniques in other behaviour problems such as wandering.^{[146][147]}

Emotion-oriented interventions include reminiscence therapy, validation therapy, supportive psychotherapy, sensory integration, also called snoezelen, and simulated presence therapy. Supportive psychotherapy has received little or no formal scientific study, but some clinicians find it useful in helping mildly impaired patients adjust to their illness.^[143] Reminiscence therapy (RT) involves the discussion of past experiences individually or in group, many times with the aid of photographs, household items, music and sound recordings, or other familiar items from the past. Although there are few quality studies on the effectiveness of RT, it may be beneficial for cognition and mood.^[148] Simulated presence therapy (SPT) is based on attachment theories and involves playing a recording with voices of the closest relatives of the person with Alzheimer's disease. There is preliminary evidence indicating that SPT may reduce anxiety and challenging behaviours.^{[149][150]} Finally, validation therapy is based on acceptance of the reality and personal truth of another's experience, while sensory integration is based on exercises aimed to stimulate senses. There is little evidence to support the usefulness of these therapies.^{[151][152]}

The aim of cognition-oriented treatments, which include reality orientation and cognitive retraining, is the reduction of cognitive deficits. Reality orientation consists in the presentation of information about time, place or person in order to ease the understanding of the person about its surroundings and his or her place in them. On the other hand cognitive retraining tries to improve impaired capacities by exertication of mental abilities. Both have shown some efficacy improving cognitive capacities,^{[153][154]} although in some studies these effects were transient and negative effects, such as frustration, have also been reported.^[143]



Three-dimensional molecular model of donepezil, an acetylcholinesterase inhibitor used in the treatment of AD symptoms



A specifically designed room for sensory integration therapy, also called snoezelen; an emotion-oriented psychosocial intervention for people with dementia

Stimulation-oriented treatments include art, music and pet therapies, exercise, and any other kind of recreational activities. Stimulation has modest support for improving behaviour, mood, and, to a lesser extent, function. Nevertheless, as important as these effects are, the main support for the use of stimulation therapies is the improvement in the person's daily life routines.^[143]

Caregiving

Further information: Caregiving and dementia

Since Alzheimer's has no cure and it gradually renders people incapable of tending for their own needs, caregiving essentially is the treatment and must be carefully managed over the course of the disease.

During the early and moderate stages, modifications to the living environment and lifestyle can increase patient safety and reduce caretaker burden.^{[155][156]} Examples of such modifications are the adherence to simplified routines, the placing of safety locks, the labelling of household items to cue the person with the disease or the use of modified daily life objects.^{[157][158][143]} The patient may also become incapable of feeding themselves, so they require food in smaller pieces or pureed.^[159] When swallowing difficulties arise, the use of feeding tubes may be required. In such cases, the medical efficacy and ethics of continuing feeding is an important consideration of the caregivers and family members.^{[160][161]} The use of physical restraints is rarely indicated in any stage of the disease, although there are situations when they are necessary to prevent harm to the person with AD or their caregivers.^[143]

As the disease progresses, different medical issues can appear, such as oral and dental disease, pressure ulcers, malnutrition, hygiene problems, or respiratory, skin, or eye infections. Careful management can prevent them, while professional treatment is needed when they do arise.^{[162][49]} During the final stages of the disease, treatment is centred on relieving discomfort until death.^[163]

Prognosis

The early stages of Alzheimer's disease are difficult to diagnose. A definitive diagnosis is usually made once cognitive impairment compromises daily living activities, although the person may still be living independently. He will progress from mild cognitive problems, such as memory loss through increasing stages of cognitive and non-cognitive disturbances, eliminating any possibility of independent living.^[50]

Life expectancy of the population with the disease is reduced.^{[8][164][165]} The mean life expectancy following diagnosis is approximately seven years.^[8] Fewer than 3% of patients live more than fourteen years.^[9] Disease features significantly associated with reduced survival are an increased severity of cognitive impairment, decreased functional level, history of falls, and disturbances in the neurological examination. Other coincident diseases such as heart problems, diabetes or history of alcohol abuse are also related with shortened survival.^{[166][164][167]} While the earlier the age at onset the higher the total survival years, life expectancy is particularly reduced when compared to the healthy population among those who are younger.^[165] Men have a less favourable survival prognosis than women.^{[9][168]}

The disease is the underlying cause of death in 70% of all cases.^[8] Pneumonia and dehydration are the most frequent immediate causes of death, while cancer is a less frequent cause of death than in the general population.^{[8][168]}

Epidemiology

AD incidence rates after 65 years of age
^[169]

Age	Incidence (new affected) per thousand person-years
65-69	3
70-74	6
75-79	9
80-84	23
85-89	40
90-	69

Two main measures are used in epidemiological studies: incidence and prevalence. Incidence is the number of new cases per unit of person-time at risk (usually number of new cases per thousand person-years); while prevalence is the total number of cases of the disease in the population at a given time.

Regarding incidence, cohort longitudinal studies (studies where a disease-free population is followed over the years) provide rates between 10–15 per thousand person-years for all dementias and 5–8 for AD.^{[169][170]} which means that half of new dementia cases each year are AD. Advancing age is a primary risk factor for the disease and incidence rates are not equal for all ages: every five years after the age of 65, the risk of acquiring the disease approximately doubles, increasing from 3 to as much as 69 per thousand person years.^{[169][170]} There are also sex differences in the incidence rates, women having a higher risk of developing AD particularly in the population older than 85.^{[170][171]}

Prevalence of AD in populations is dependent upon different factors including incidence and survival. Since the incidence of AD increases with age, it is particularly important to include the mean age of the population of interest. In the United States, Alzheimer prevalence was estimated to

be 1.6% in the year 2000 both overall and in the 65–74 age group, with the rate increasing to 19% in the 75–84 group and to 42% in the greater than 84 group.^[172] Prevalence rates in less developed regions are lower.^[173] The World Health Organization estimated that in 2005, 0.379% of people worldwide had dementia, and that the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030.^[174] Other studies have reached similar conclusions.^[173] Another study estimated that in 2006, 0.40% of the world population (range 0.17–0.89%; absolute number 26.6 million, range 11.4–59.4 million) were afflicted by AD, and that the prevalence rate would triple and the absolute number would quadruple by the year 2050.^[2]

History

The ancient Greek and Roman philosophers and physicians associated old age with increased dementia.^[175] It was not until 1901 that German psychiatrist Alois Alzheimer identified the first case of what became known as Alzheimer's disease in a fifty-year-old woman he called Auguste D. Alzheimer followed her until she died in 1906, when he first reported the case publicly.^[176] During the next five years, eleven similar cases were reported in the medical literature, some of them already using the term Alzheimer's disease.^[175] The disease was first described as a distinctive disease by Emil Kraepelin, who included *Alzheimer's disease*, also named *presenile dementia* by Kraepelin, as a subtype of *senile dementia* in the eighth edition of his *Textbook of Psychiatry*, published in 1910.^[177]



Auguste D, first described patient with AD by Alois Alzheimer in 1901

For most of the twentieth century, the diagnosis of Alzheimer's disease was reserved for individuals between the ages of 45 and 65 who developed symptoms of dementia. The terminology changed after 1977 when a conference on AD concluded that the clinical and pathological manifestations of presenile and senile dementia were almost identical, although the authors also added that this did not rule out the possibility of different aetiologies.^[178] This eventually led to the diagnosis of *Alzheimer's disease* independently of age.^[179] The term *senile dementia of the Alzheimer type* (SDAT) was used for a time to describe the condition in those over 65, with classical Alzheimer's disease being used for those younger. Eventually, the term Alzheimer's disease was formally adopted in medical nomenclature to describe individuals of all ages with a characteristic common symptom pattern, disease course, and neuropathology.^[180]

Society and culture

Social costs

Dementia, and specifically Alzheimer's disease, may be among the most costly diseases for society in the developed countries,^{[177][18]} while their cost in developing countries such as Argentina,^[181] or Korea,^[182] is also high and rising. These costs will probably increase with the ageing of society, becoming an important social problem. AD associated costs include direct medical costs such as nursing home care, direct nonmedical costs such as in-home day care, and indirect costs such as lost productivity of both patient and caregiver.^[18] Numbers vary between studies but dementia costs worldwide have been calculated around \$160 billion,^[183] while costs of Alzheimer in the United States may be \$100 billion each year.^[18]

The greatest origin of costs for society is the long-term care by health care professionals and particularly institutionalisation, which corresponds to 2/3 of the total costs for society.^[17] The cost of living at home is also very high,^[17] specially when informal costs for the family, such as caregiving time and caregiver's lost earnings, are taken into account.^[184]

Costs increase with dementia severity and the presence of behavioural disturbances,^[185] and are related to the increased caregiving time required for the provision of physical care.^[184] Therefore any treatment that slows cognitive decline, delays institutionalisation or reduces caregivers' hours will have economic benefits. Economic evaluations of current treatments have shown positive results.^[18]

Caregiving burden

Further information: Caregiving and dementia

The role of the main caregiver is often taken by the spouse or a close relative.^[186] Alzheimer's disease is known for placing a great burden on caregivers which includes social, psychological, physical or economic aspects.^{[14][15][16]} Home care is usually preferred by patients and families.^[187] This option also delays or eliminates the need for more professional and costly levels of care.^{[188][187]} Nevertheless two-thirds of nursing home residents have dementias.^[143]

Dementia caregivers are subject to high rates of physical and mental disorders.^[189] Factors associated with greater psychosocial problems of the primary caregivers include having an affected person at home, the carer being a spouse, demanding behaviours of the cared person such as depression, behavioural disturbances, hallucinations, sleep problems or walking disruptions and social isolation.^{[190][191]} Regarding economic problems, family caregivers often give up time from work to spend 47 hours per week on average with the person with AD, while the costs of caring for them are high. Direct and

indirect costs of caring for an Alzheimer's patient average between \$18,000 and \$77,500 per year in the United States, depending on the study.^{[192][184]}

Cognitive behavioural therapy and the teaching of coping strategies either individually or in group have demonstrated their efficacy in improving caregivers' psychological health.^{[144][193]}

Notable cases

Further information: Alzheimer's in the media

As Alzheimer's disease is highly prevalent, many notable people have developed it. Well-known examples are former United States President Ronald Reagan and Irish writer Iris Murdoch, both of whom were the subjects of scientific articles examining how their cognitive capacities deteriorated with the disease.^{[194][195]} Other notable cases include the retired footballer Ferenc Puskas,^[196] the former Prime Ministers Harold Wilson (Great Britain) and Adolfo Suárez (Spain),^{[197][198]} the actress Rita Hayworth,^[199] the actor Charlton Heston,^[200] and the novelist Terry Pratchett.^[201]



Charlton Heston and Ronald Reagan at a meeting in the White House. Both of them would later develop Alzheimer's disease.

AD has also been portrayed in films such as: *Iris* (2001),^[202] based on John Bayley's memoir of his wife Iris Murdoch;^[203] *The Notebook* (2004),^[204] based on Nicholas Sparks' 1996 novel of the same name;^[205] *Thammasatra* (2005),^[206] *Memories of Tomorrow* (*Ashita no Kioku*) (2006),^[207] based on Hiroshi Ogiwara's novel of the same name;^[208] and *Away from Her* (2006), based on Alice Munro's short story "The Bear Came over the Mountain".^[209] Documentaries on Alzheimer's disease include *Malcolm and Barbara: A Love Story* (1999) and *Malcolm and Barbara: Love's Farewell* (2007), both featuring Malcolm Pinton.^[210]

Research directions

As of 2008, the safety and efficacy of more than 400 pharmaceutical treatments are being investigated in clinical trials worldwide, and approximately one-fourth of these compounds are in Phase III trials, which is the last step prior to review by regulatory agencies.^[211]

One area of clinical research is focused on treating the underlying disease pathology. Reduction of amyloid beta levels is a common target of compounds under investigation. Immunotherapy or vaccination for the amyloid protein is one treatment modality under study. Unlike preventative vaccination, the putative therapy would be used to treat people already diagnosed. It is based upon the concept of training the immune system to recognise, attack, and reverse deposition of amyloid, thereby altering the course of the disease.^[212] An example of such a vaccine under investigation was ACC-001,^{[213][214]} although the trials were suspended in 2008.^[215] Similar agents are bapineuzumab, an antibody designed as identical to the naturally-induced anti-amyloid antibody,^[216] and MPC-7869, a selective amyloid beta-42 lowering agent.^[217] Other approaches are neuroprotective agents, such as AL-108,^[218] and metal-protein interaction attenuation agents, such as PBT2.^[219] A TNFα receptor fusion protein, etanercept has showed encouraging results.^[220]

In 2008, two separate clinical trials showed positive results in modifying the course of disease in mild to moderate AD with methylthioninium chloride (trade name *rember*), a drug that inhibits tau aggregation,^{[221][222]} and dimebon, an antihistamine.^[223]

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